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Editorial: 'cMyC - how a novel biomarker could transform chest pain triage'

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Editorial: 'cMyC - how a novel biomarker could transform chest pain triage'

Chest pain is a common symptom – according to recent literature it is responsible for at least 6% of all presentations to emergency departments – however, only about 10% of these patients have a final diagnosis of Acute Myocardial Infarction (AMI).[1–5] Chest pain triage is fraught with difficulties as physicians are increasingly caught at the interplay of sensitivity and specificity: Fewer patients now have the diagnostic electrocardiogram (ECG) changes of ST-elevation or depression that allow triage at presentation [6,7] – in fact, 68% of all patients eventually diagnosed with an acute coronary syndrome (ACS) present with Non-ST elevation myocardial infarction (NSTEMI).[8] Consequently, triage has become reliant on the elevation in the blood of the biomarker cardiac Troponin (cTn). This is enshrined in the Universal Definition of Myocardial Infarction [9] and guidelines published by the European Society of Cardiology (ESC) [10], mandating the detection of a cardiac biomarker rise and/or fall for the diagnosis of AMI.

The challenging reality of chest pain triage

The technological advances in evolving cTn assays to high-sensitivity tests comes at the expense of loss of specificity; as analysers are increasingly able to provide quantifiable cTn levels in almost every individual.[11,12] The very definition of a hs-cTn assay – according to the International Federation of Clinical Chemistry and Laboratory Medicine Task Force on Clinical Applications of cardiac Bio-Markers (IFCC TF-CB) – includes 1) a Coefficient of Variation (CV) $\leq$10% at the 99th centile value and 2) the ability to measure at least 50% of healthy individuals with concentrations above the assay's Limit of Detection (LoD).[13,14] The clinical reality of this advance in assay-

technology is that many more patients test ‘Troponin-positive’, but not necessarily ‘AMI-positive’ – all in an attempt to overcome the limitations which made cTn inherently unsuited for early diagnosis of acute myocardial injury: a slow rise and disappearance from the blood stream after myocardial injury.[15,16] By the ESC’s own admission, the clinical implications of using high-sensitivity (hs) cTn assays include a 2-fold increase of detection of type 2 AMI, ~20% relative increase in detection of type 1 AMI and ‘elevations up to 3-fold the upper reference limit (URL)…may be associated with a broad spectrum of conditions’.

Sensitivity comes at a cost

The emergency physician is caught up in this sensitivity/specificity quagmire: they have to handle complex rule-in/rule-out algorithms to optimise care for the patient with suspected Acute Coronary Syndrome (ACS) at the front-door of the hospital.[10,17] Two aspects make this inherently more challenging: 1) Even with high-sensitivity assays, the ESC advocates a delay of 3 hours after chest pain onset for the first blood draw to take place; 2) Many patients get caught up in an ‘observe’ zone of indeterminate risk – too high a cTn level for discharge, but too low to classify as AMI. Without doubt, evermore-sensitive assays will establish a new reality of biomarker-interpretation in acute medical services around the world – the (nearly) always-quantifiable level of a cardiac biomarker ought to be scrutinised in the context of the clinical presentation, and we can no longer rely on an outdated black & white approach. But maybe we can achieve more effective triage using a highly-sensitive and specific biomarker with a more favourable release profile?

There might be another way…

Cardiac myosin-binding protein C (cMyC) is a promising novel biomarker of myocardial injury – originally described as the C-protein by Offer et al. in 1973 [18], its discovery relied on the characterisation of 'impurities' detected alongside myosin. cMyC has distinctive release-kinetics that should enable it to act as a better adjudicator of acute versus chronic myocardial injury than Troponin.[19] We have raised monoclonal antibodies targeting the cardiac isoform of myosin-binding protein C and successfully migrated the assay onto a high-sensitivity platform.[12] Subsequently, we demonstrated up to 10-fold greater abundance of cMyC after myocardial injury than two leading hs-cTnT/I assays.[20] In a small study involving 174 patients presenting within 3 hours of chest pain onset and suspected AMI, we demonstrated a more dynamic rise of cMyC in the early stages of AMI than hs-cTnI.[21] This faster rise ought to yield a positive result (for rule-in of AMI), or an earlier reliable negative result (for rule-out of AMI). Furthermore, the relative abundance of cMyC should allow careful calibration of rule-out and rule-in thresholds, with more 'headroom' to enable precise quantification at the low concentrations needed for rule-out.

Large chest pain study confirms efficacy

This hypothesis was tested in a study of >1,900 patients with symptoms suggestive of AMI – in an internal derivation/validation split, we derived cut-off thresholds for immediate rule-out or rule-in of AMI using cMyC instead of hs-cTnT/I (modelled on the 2015 ESC NSTEMI guideline).[10,22] At similar diagnostic accuracy (based on comparable area under the receiver-operating characteristics curve), cMyC was substantially more effective than either hs-cTn assay in guiding

patients to (safe) rule-out or rule-in: the net reclassification improvement demonstrated 14.9-23.5% better triage efficiency, thus reducing the size of the 'observe' zone substantially. Based on an institution such as St Thomas' Hospital, a central London hospital home to a tertiary cardiac unit, about 7,800 patients are subject to hs-cTnT testing in the Emergency Department annually. [23] Our findings would translate into savings of 1,000 bed days per year – simply by achieving a more effective triage with a single blood draw at presentation.

Faster, better…Point-of-Care?

But, there is an even greater goal to aim for: point-of-care testing (POCT) of cardiac biomarkers. To date, there is no POCT device that can achieve the levels of sensitivity required to provide accurate measurement of troponin for rule-out of AMI. This task requires a POCT assay to achieve a limit of detection equivalent to the laboratory assay, as the ESC guidelines advocate rule-out only in patients with undetectable hs-cTn levels. The best cTnT POCT platform (Roche Cobas h323 handheld instrument) can detect a laboratory-equivalent value of 50 ng/L – about 3.5-fold greater than the 99th centile, or 10-fold the LoD of the laboratory assay.[24] While not bioequivalent, it is tempting to speculate whether cMyC – with a 10-fold greater abundance, and a rule-out threshold 25-fold the LoD of the current laboratory platform – might facilitate easier migration onto a handheld device. This would allow rapid deployment of a novel cardiac biomarker to secondary and tertiary care facilities, and pave the way to a cluster-randomised controlled trial. Such a trial, with ethical consent at institutional level to ensure rapid enrolment of a large number of participants, would allow – for the first time – a head-to-head comparison of the effectiveness of different cardiac biomarkers in acute chest pain triage. The potential advantages are compelling: as most

patients presenting with chest pain do not have AMI, the goal must be to rule-out AMI in as many patients as possible at the earliest opportunity – i.e. with the first blood draw. Even better, if this could be facilitated in a pre-hospital setting, where cMyC seems to benefit from dynamic release kinetics.[25] cMyC might allow earlier rule-out of AMI [22], and if the promise of more effective triage holds true, up to a fifth of all patients could benefit from expedited discharge, or care where necessary.

In conclusion, cMyC is a cardiac-restricted protein which rapidly enters the systemic circulation after myocardial injury and is relatively more abundant than troponin. The biomarker performs favourably in the diagnosis of AMI and is particularly well-suited to a point-of-care diagnostic platform – which could transform the way we perform chest pain triage.

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Prof Marber is named as an inventor on a patent held by King’s College London for the detection of cardiac myosin–binding protein C as a biomarker of myocardial injury.

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